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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,917	TEHIM ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-14 and 20-34* is/are pending in the application.

4a) Of the above claim(s) *14 and 22-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-13,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in United Kingdom on 5-27-1997 and 10/21/1996. Applicant has submitted certified copies of the foreign applications with the last response.

Election/Restrictions

2. Claims 1-7, 9-19, 20-34 are pending. Claim 8 has been canceled according to the amendment filed on 7-12-2002. Claims 14-19 are withdrawn from further consideration as being drawn to the non-elected invention.

Applicant requests that claims 14-19 be considered as they are drawn to a single inventive concept. On the contrary, the application contains claims to more than one of the combination of categories of invention since it contains 6 different alternative processes of use. The restriction as indicated is therefore improper.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re*

Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. Newly submitted claims 22-34 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 22-34 are method claims for treating different types of pain, which would be grouped with Group II, claim 14, drawn to the method of treating pain.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 22-34 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Double Patenting

4. The obviousness-type double patenting rejection over the corresponding claims of US Patent No. 6492380 is replaced by the obviousness-type double patenting rejection over US Patent No. 6492380 in view of Bundgaard as set forth in paragraph below.

Claim Rejections - 35 USC § 103

5. The rejection for Claims 1-4, 9-12 under 35 U.S.C. 103(a) as being unpatentable over Sestanj I (3821383, PTO-1449) in view of Malizia (EP 206322, PTO-1449) is replaced by the 103 rejection over Sestanj I (3821383, PTO-1449) in view of Malizia and Bundgaard set forth in paragraph below.

Claim Rejections - 35 USC § 112

6. The rejection for Claims 1-4, 9-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The compound in proviso (ii), i.e. the compound wherein when R3 is nitro, R1 is benzyl is not described in the specification. The concept that when R3 is a certain substituent then R1 is a certain substituent is not taught or described in the specification. Furthermore, R1 as benzyl is not described in any of the Examples.

Claim Rejections - 35 USC § 112

7. The rejection for Claims 5, 6, 13 under 35 U.S.C. 112, second paragraph set forth in the previous office action is withdrawn in view of the amendment obviating the rejection.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1-7, 9-12, 14, 20, 21 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. A composition comprising the NGF antagonist, ALE-0540 (N-{5-nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol) and its use for treating a NGF-mediated activity is the invention of Owolabi et al. (Journal of Pharmacology and Experimental Therapeutics. 1999, 289 (3): 1271-1276, PTO-1449 AX).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-7, 9, 20, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over reference AZ2 (PTO-1449; and the information data sheet on the compound provided by Ryan Scientific, Inc.) in view of Gray et al (Analytical Biochemistry, 199, 216(1): 89-96, abstract) and/or Kubinyi (Die Pharmazie, (1995 Oct) 50 (10) 647-62, abstract)

The inventive compound, N-{5-nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol, has been on sale as product 'PHG 01006' of Ryan Scientific, Inc. since 1973 as a compound for high throughput screening www.ryansci.com (PTO-1449, AZ2; see information data sheet provided by Ryan Scientific). High throughput screening for drugs is well known in the art (Gray, abstract; Kubinyi, abstract). It would be obvious to the skill person in the art to prepare a composition comprising the compound for high throughput screening of drugs. For a composition claim, the intended use fails to set a demarcation from the prior art composition comprising the same compound.

11. Claims 5, 6, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brana III (4874863, PTO-1449) in view of Bundgaard.

Brana generically discloses a bisnaphthalimide with cytotoxic activity (column 1), and the pharmaceutical composition thereof. A specific compound is described (column 3, Example 4).

The prior art compound has a nitro whereas the instant 3-amino-7, 4-bis (ethyl-l,3-dioxo)-1, 2 ,3,4-tetrahydrobenzo[i]isoquinoline, has a hydrogen on the aromatic portion of the molecule.

However, Brana teaches that nitro and hydrogen are optional substituents leading to an effective anti-tumor compound (column 1, lines 29-30).

At the time of the invention, one of ordinary skill in the art would be motivated to prepare a pharmaceutical composition comprising a compound with a hydrogen instead of nitro as in Brana's example compound to arrive at the instant invention with the reasonable expectation of obtaining and additional anti-tumor composition.

While Brana does not specifically discloses the in vivo hydrolysable amide or ester of the example compound as in the instant claim 13, Bundgaard teaches that ester or amide is art-recognized prodrug (page 2, 27).

At the time of the invention, one of ordinary skill in the art would be motivated to prepare the ester or amide prodrug of Brana's compound as taught by Bundgaard to arrive at the instant invention with the reasonable expectation of enhancing the delivery of the drug compound.

12. Claims 1-4, 9-12, are rejected under 35 U.S.C. 103(a) as being unpatentable over Sestanj I (3821383, PTO-1449) in view of Malizia (EP 206322, PTO-1449) and Bundgaard.

Sestanji discloses a benzoisoquinoline compound, and the composition thereof, useful for treating diabetic neuropathy. A specific compound, 5-nitro- 1,3-dioxo-1H-benz[de]isoquinoline-2(H)-acetic acid, is described (column 4, table).

Sestanji 's compound has an acetic acid moiety whereas the instant compound, has a propionic acid moiety. The instant propionic acid is therefore the next adjacent homolog of Sestanji's acetic acid.

Malizia specifically teaches that compound I, the propionic acid homolog of Sestanji's compound, is more active and endowed with more advantageous pharmaco-therapeutic characteristics (page 2, lines 12-19).

At the time of the invention, one of ordinary skill in the art would be motivated to prepare the composition comprising the more active propionic acid compound as taught by Malizia in place of Sestanji' acetic acid compound to arrive at the instant invention with the reasonable expectation of obtaining a more effective composition for treatment of neuropathy.

Sestanji does not describe the ester or amide of the example compound as in the instant. However, the instant loweralkoxycarbonyl (i.e. ester) is art-recognized prodrug for the carboxy group, which is expressly taught by Bundgaard (page 2, 27).

At the time of the invention, one of ordinary skill in the art would be motivated to prepare the ester prodrug of the prior art compound as taught by Bundgaard to arrive at the instant invention with the reasonable expectation of enhancing the delivery of the drug compound.

Duplicate Claims

13. Claim 9 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 9-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 6492380 in view of Bundgaard. The instant compound is the prodrug (i.e. alkoxycarbonyl ester) of the carboxy compound in the patent.

However, the instant loweralkoxycarbonyl (i.e. ester) is art-recognized prodrug for the carboxy group, which is expressly taught by Bundgaard (page 2, 27). At the time of the invention, one of ordinary skill in the art would be motivated to prepare the ester prodrug of the patended compound as taught by Bundgaard to arrive at the instant invention with the reasonable expectation of enhancing the delivery of the drug compound.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-13, 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-7, 9-12, the term 'mediated' in 'neurotropin-mediated activity' is unclear since 'mediated' does not distinguish between the activity resulting from activation and the activity resulting from the inhibition of neurotropin.

b. Claim 13, what are the substituents on the ester or amide? A full definition of their chemical structure is not found in the specification.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-12, 21 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The 'neurotropin-mediated activity' encompasses conflicting conditions or diseases and reaches out to conditions or diseases not yet discovered. A full description of 'the neurotropin-mediated activity' is not described in the specification.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-12, 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the composition comprising the inventive compound for treating pain, does not reasonably provide enablement for treatment of any 'neurotropin-mediated activity'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

a. *Nature of the invention.*

The instant invention is drawn to a naphthaimide compound for inhibiting neurotropin-mediated activity.

b. *State of the prior art and the level of the skill in the art.*

The neurotropin family includes NGF, neurotropin 3 and neruotrophin 4/5. Two cell surface receptors for NGF have been characterized only recently and small peptide mimics of NGF have been prepared (LeSauteur et al. The Journal of Biochemistry, 1995, 270(12): 6564-69). A substituted pyrazoloquinazolinone compound has been shown to inhibit the NGF binding (Jaen, 5342942, PTO-1449). Although many diseases have been implicated, the nexus between the inhibition of neurotropin and the treatment of all the recited diseases or conditions has not been fully established.

The level of the skill in the neurotropin inhibitor art is high.

c. *Predictability/unpredictability of the art.*

The high degree of unpredictability is well-recognized in the pharmaceutical art. A slight modification of the compound would drastically change its biological activity (Jaen, columns 14-15, Table I). Structural requirements for binding to the receptor are absolute (LeSauteur, abstract; page 6567, Table II, Table III). Since a correlation between the inhibition of NGF binding and the biological response has not been fully established, one of ordinary skill in the art would have

little basis to extrapolate the binding data to various in vivo situations involving different target tissues.

d. *Amount of guidance/working examples.*

How to make

The preparation of N-{5-nitro-1H-benz[de]isoquinoline-1,3(2H)-dione}-2-aminoethanol has been described on page 26. An example of an in vivo hydrolysable ester or amide of the compound as claimed has not been shown. The process for making these compounds are not found in the specification.

How to use

The procedures for assessing the inhibition of NGF binding and the inhibition of neurite outgrowth are described in Examples 1 and 2. The results are shown in Tables 1 and 2 (for compound A only) respectively. The animal models of neuropathic pain are described in Example 3, and the results for compound A shown in Table 4.

e. *The breadth of the claims.*

Applicant's assertion that all the inventive compounds would be effective in treating any neurotropin-mediated activity (including the conflicting conditions or diseases and those not yet discovered conditions or diseases), does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the art, and the limited working examples (paragraphs b-d above).

f. *Amount of undue experimentation.*

Since insufficient teaching and guidance have been provided in the specification (paragraphs b-e above), one of ordinary skill in the art, even with high degree of skill, would not be able to make and use the inventive compounds as claimed without undue experimentation except for using the inventive compound for treating pain.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Evelyn Huang
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